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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/717,450	11/20/2000	Lisa Ann Neuhold	0630/D532US1	5417

7590 01/30/2002

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1633	5

DATE MAILED: 01/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/717,450	Applicant(s) NEUHOLD ET AL.	
	Examiner Michael Wilson	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: detailed action/notice to comply.

DETAILED ACTION

The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Claims 1-27 have been canceled. Claims 28-54 have been added and are under consideration in the instant office action.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **Fig. 1A has an amino acid sequence in the Pre/Pro domain and in the Catalytic domain - each should be described in the description of Fig. 1A with a SEQ ID NO (page 8, line 6). The description of the nucleic acid in Fig. 1B on page 8, line 14 does not have a SEQ ID NO.** Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Applicant is requested to return

a copy of the attached Notice to Comply with the reply. For a response to the instant office action to be considered fully responsive, applicants must fully comply with the sequence rules.

Information Disclosure Statement

The IDS filed 2-28-01 is improper because the citations are incomplete. The US Patent does not have the date, name, class or subclass. The Foreign patents information is in the wrong area or missing. The citation, DE 19501032A1, has not been considered because a translation has not been provided. Most of the other references lack a title and many do not have a date of publication.

Claim Objections

Please put a comma between "constitutively" and "enzymatically active..." when they occur together (claims 30, 31, et al.).

The preamble of claims 28 and 41 should be as follows: "A transgenic... [mouse] ...whose genome comprises...."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 28-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

An adequate written description of a transgenic non-human mammals having a characteristic of osteoarthritis requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the combination of DNA encoding an extracellular matrix enzyme, chondrocyte-specific promoter, and the method of making transgenic non-human mammals required to obtain a transgenic non-human mammal having a characteristic of osteoarthritis. It is not sufficient to define the transgenic solely by its phenotype, i.e. a characteristic of osteoarthritis, because disclosure of no more than that, as in the instant case, is simply a wish to identify transgenics in the future having a characteristic of osteoarthritis. Also, naming a transgenic non-human mammal having a characteristic of osteoarthritis in the absence of knowledge as to the DNA encoding an extracellular matrix enzyme, the chondrocyte-specific promoter, and the method of making the transgenic, is not a description of that material. Thus, claiming all transgenic non-human mammals having a characteristic of osteoarthritis without defining the combination of DNA encoding an extracellular matrix enzyme, chondrocyte-specific promoter, and the method of making transgenic non-human mammals required is not in compliance with the description requirement.

The phrase "chondrocyte tissue-specific promoter" lacks written description because the specification does not disclose any promoters that cause expression exclusively in chondrocytes. For example, the specification and the art do not teach the Type II collagen promoter is expressed only in chondrocytes or teach the expression pattern of Type II collagen promoter in non-chondrocytes. Without such guidance, the specification does not provide adequate written description for any "chondrocyte tissue-specific promoter" as claimed. An adequate written description of a "chondrocyte tissue-specific promoter" requires more than a mere statement that it is part of the invention. What is required is a description of the promoter itself. It is not sufficient to define a promoter as being "chondrocyte-specific" because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of promoters that function only in chondrocytes or only in a specific type of chondrocyte. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, the limitation of promoters that are "chondrocyte-specific" without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

The specification does not provide adequate written description for using any and all sequences of SEQ ID NO:1 or 21 in the instant invention (claim 32). The specification and the art at the time of filing does not teach any fragments of SEQ ID NO:1 or 21 having equivalent

function to full length sequences of SEQ ID NO:1 or 21. Thus, claiming all sequences within SEQ ID NO:1 or 21 without defining what fragments have equivalent function will do is not in compliance with the description requirement.

Likewise, the specification does not provide adequate written description for using any and all sequences of a tet07 sequence (claim 37), SEQ ID NO:2 (claim 38), a Type II collagen promoter (claim 39, 42), in the instant invention. The specification and the art at the time of filing do not teach any fragments of tet07, SEQ ID NO:2, or Type II collagen promoter having equivalent function to full length sequences. Thus, claiming all sequences within tet07, SEQ ID NO:2, or Type II collagen promoter lacks written description.

The specification does not provide adequate written description for more than one species of transcriptional repressor protein (claim 28), transcriptional activator protein (claim 28), tetracycline repressor protein (claim 36), Type II collagen promoter (claim 39, 42), tet07 promoter (claim 42), tTA polypeptide (claim 42). The specification and the art at the time of filing do not teach more than one species of such materials. Thus, a claim having a limitation encompassing any and all transcriptional repressor or activator proteins, tetracycline repressor proteins, Type II collagen promoters or tet07 promoters lacks written description.

The specification does not provide adequate written description for tTA that is a tetracycline repressor (claim 42). The specification teaches tTA is used as a tetracycline activator. The diagrams provided illustrating the tet inducible and repressible system both say tTA is a tet activator. Clarification is required.

The specification does not provide adequate written description for any repressible system other than the tet repressible system. The specification and the art do not teach any other repressible systems, specifically repressible systems used in transgenics. The ecdysone and RU486 systems are inducible. Therefore, claims limited to repressible systems should be limited to the tet repressible system.

2. The phrase "chondrocyte tissue-specific promoter" is new matter. While the specification mentions obtaining selective expression of MMP in join tissues, preferably in articular chondrocytes (page 6, line 4; page 13, line 3) and obtaining tissue-specific expression using the Type II collagen promoter (page 37, line 1), the citations do not support the limitation of "chondrocyte tissue-specific promoter." The specification does not teach Type II collagen promoter or any other promoter is exclusively expressed in chondrocytes. The specification does not state selective expression of MMP in join tissues, preferably in articular chondrocytes is dependent upon the promoter. Therefore, the phrase "chondrocyte tissue-specific promoter" is new matter.

3. Claims 28-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively, enzymatically active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a

nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause a characteristic of osteoarthritis, does not reasonably provide enablement for any non-human mammal, any "matrix degrading enzyme that degrades an extracellular matrix component," or any "chondrocyte tissue-specific promoter." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are not enabled as broadly written because the specification does not provide adequate guidance for one of skill to obtain a characteristic of osteoarthritis in any transgenic non-human mammal using any "chondrocyte-specific promoter" and any matrix degrading enzyme. The state of the art at the time of filing was that it was unpredictable how to obtain the phenotype of interest in transgenics. The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats

expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989; Taurog, 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Thus, the combination of elements (protein, promoter, species of protein, and species of transgenic) required to obtain a desired effect were not within the realm of routine experimentation at the time of filing. The art at the time of filing also taught that attempts to engineer transgenic animals expressing MMP, e.g. MMP1 and stromelysin have not resulted in joint degeneration (page 4, line 15). As such the combination of protein, promoter, and species of transgenic required to obtain a characteristic of osteoarthritis were unpredictable at the time the invention was made.

The specification teaches making a transgenic mouse whose genome comprises: a) a nucleotide sequence encoding a constitutively, enzymatically active, human MMP that cleaves Type II collagen, wherein the nucleotide sequence is operatively linked to a regulatable promoter; and b) a nucleotide sequence encoding a transcription activator or repressor protein operatively linked to a Type II collagen promoter, wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mouse. Expression is controlled by the administration/withdrawal of tetracycline or other regulatory compound.

The specification teaches other proteins that degrade "extracellular matrix" (page 2-3). The specification does not provide adequate correlation between constitutively, enzymatically active, human MMP that degrades Type II collagen and other proteins to enable any enzymatically active matrix degrading enzyme that degrades an extracellular matrix component. The specification states the enzymes encoded by the transgene are enzymatically latent and require proteolytic processing. The specification does not teach how to control such processing in transgenics and obtain a characteristic of osteoarthritis without making the protein constitutively active. Therefore, the protein claimed should be constitutive active (page 11, line 22 through page 12, line 12). The specification does not correlate MMPs that degrade Type II collagen to other enzymes such that any enzyme that degrades extracellular matrix could be used to obtain a characteristic of osteoarthritis. The specification does not teach obtaining adequate expression or degrading the tissue of interest using any enzyme that degrades extracellular matrix such that a characteristic of osteoarthritis was obtained. Therefore, the claims should be limited to MMP that degrades Type II collagen. The specification does not correlate human MMP that degrades Type II collagen with other species of MMP such that equivalent expression or function would be obtained. The specification does not enable any enzyme that degrades extracellular matrix other than human enzymes because, without evidence to the contrary, human enzymes that degrade extracellular matrix are structurally and functionally different than non-human enzymes. Therefore, the enzyme should be limited to human enzymes. In conclusion, the

enzyme should be limited to constitutively, enzymatically active, human MMP that degrades Type II collagen.

The specification teaches the Type II collagen promoter and mentions obtaining selective expression of MMP in join tissues, preferably in articular chondrocytes. The specification does not teach any promoters related to chondrocytes, any chondrocyte-specific promoters or any means of obtaining expression preferably in the articular chondrocytes. The art did not teach a transgenic having a chondrocyte-specific promoter and a characteristic of osteoarthritis. While some promoters related to chondrocytes were known in the art, the art and the specification do not teach using such promoters in transgenics. In addition, a number of promoters were known in the art that functioned in transgenics; however, they were not chondrocyte-specific, used to degrade extracellular matrix or used to obtain a characteristic of osteoarthritis. Therefore, the specification does not enable using any chondrocyte-specific promoter as broadly claimed to obtain a characteristic of osteoarthritis. Given the unpredictability in the art taken with the lack of teachings in the specification and the art, it would have required one of skill undue experimentation to determine how to use any chondrocyte-specific promoter to target the tissue of interest, degrade the tissue of interest and obtain a characteristic of osteoarthritis.

The specification contemplates making other transgenic non-human mammals (page 22, line 15). Not only is the difference in transgenic mice and rats unpredictable for reasons stated above, the art at the time of filing was such that a number of significant limitation regarding the production of non-mouse transgenic animals existed. Wall (1996, Theriogenology, Vol. 45,

pages 57-68) disclosed the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Ebert (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (page 277, column 2, lines 17-27). Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, method used and phenotype obtained were required to make a transgenic non-human mammal of interest. The art at the time of filing did not teach any transgenic non-human mammal expressing a matrix degrading enzyme, having a chondrocyte-specific promoter or having a characteristic of osteoarthritis. Given the difference in expression, specificity of promoters and phenotypes between mice and rats, taken with the unpredictability regarding obtaining transgenics other than mice, the unpredictability regarding the parameters required to obtain a phenotype of interest in transgenics and the lack of guidance provided in the specification regarding how to obtain transgenics other than mice and the lack of guidance

provided in the specification regarding how to obtain characteristics of osteoarthritis in mammals other than mice, the specification does not enable making any transgenic non-human mammal having a characteristic of osteoarthritis as broadly claimed.

The specification does not enable using any and all sequences of SEQ ID NO:1 or 21 (claim 32), a tet07 sequence (claim 37), SEQ ID NO:2 (claim 38), or a Type II collagen promoter (claim 39, 42), in the instant invention. The specification and the art at the time of filing do not teach any fragments of SEQ ID NO:1 or 21, tet07, SEQ ID NO:2, Type II collagen promoter having equivalent function to full length sequences. The specification does not teach an assay to determine fragments of SEQ ID NO:1 or 21, tet07, SEQ ID NO:2, Type II collagen promoter having the desired function. It would require one of skill to determine fragments of SEQ ID NO:1 or 21, tet07, SEQ ID NO:2, Type II collagen promoter having equivalent function as full length sequences or that could be used in the claimed invention.

The specification does not any transcriptional repressor protein (claim 28), transcriptional activator protein (claim 28), tetracycline repressor protein (claim 36), Type II collagen promoter (claim 39, 42), tet07 promoter (claim 42), tTA polypeptide (claim 42) as broadly claimed. The specification and the art at the time of filing do not teach more than one transcriptional repressor protein, transcriptional activator protein, tetracycline repressor protein, Type II collagen promoter, tet07 promoter, or tTA polypeptide. It would require one of skill to determine other transcriptional repressor protein, transcriptional activator protein, tetracycline repressor protein,

Type II collagen promoter, tet07 promoter, or tTA polypeptide having equivalent function or that could be used in the claimed invention.

The specification does not enable using tTA as a tetracycline repressor (claim 42). The specification teaches tTA is used as a tetracycline activator. The diagrams illustrating the tet repressible system and inducible system both state tTA is a tetracycline activator.

The specification does not enable using any repressible system in transgenics other than the tet repressible system. The specification and the art do not teach any other repressible systems, specifically repressible systems used in transgenics. The ecdysone and RU486 systems are inducible. Therefore, claims limited to repressible systems should be limited to the tet repressible system.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 28-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28 and 41 are indefinite because the phrase "expression of the MDE by chondrocytes is repressed throughout embryonic, fetal, and early postnatal development, and activation of expression of the MDE results in a phenotypic change characteristic of osteoarthritis" is unclear.

The phrase is not directly linked to the transgenic mammal; therefore, it cannot be determined whether "expression," the "embryonic, fetal, and early postnatal development" or the "activation" in the phrase occurs in or correlates to the transgenic mammal.

It cannot be determined if applicants intend to claim a mammal capable of having a characteristic of osteoarthritis or a mammal having a characteristic of osteoarthritis. Mammals having a characteristic of osteoarthritis are a subset of mice capable of having a characteristic of osteoarthritis. Is the mammal claimed expressing MDE? Does it have a characteristic of osteoarthritis? The metes and bounds of mammals encompassed by the claims cannot be determined.

The phrase "early postnatal development" is indefinite because the metes and bounds of what applicants consider "early" cannot be determined and does not have an art accepted meaning.

The distinction between "embryonic" and "fetal" development cannot be determined. The metes and bounds of what applicants consider "embryonic" and "fetal" cannot be determined and does not have an art accepted meaning.

The phrase "phenotypic change characteristic of osteoarthritis" is unclear. It is unclear whether applicants intend to claim a mammal over a period of time as it develops a characteristic of osteoarthritis or a mammal having a characteristic of osteoarthritis.

The phrase "without proteolytic processing" (claim 30) is unclear and should be deleted.

The phrase "constitutively enzymatically active MMP-13 variant" (claims 31 and 32) is unclear. Is the variant no longer constitutively or enzymatically active? Is the MMP-13 made constitutively enzymatically active and further varied? The metes and bounds of MMP-13 variants encompassed by the phrase cannot be determined. Deletion of "variant" is suggested.

Claim 35 is indefinite because if the protein is a repressor, it cannot be an activator. The phrase "...wherein the polypeptide is a transcriptional repressor." may overcome this rejection. It is noted that "a transcriptional repressor polypeptide" lacks written description (see above).

Claims 40, 45, 48, 51 are indefinite because the genus of the Markush group uses the singular form while species within the Markush group use the plural form. Furthermore, how "gross" is "gross" observation? The metes and bounds of "gross" cannot be determined. Please change "gross observations of changes...", "changes in growth plate..." and "osteophyte formation and combinations thereof" to "a change in joint function...", "a change in growth plate..." and "osteophyte formation, and a combination thereof."

Claim 44 is indefinite. Claim 44 may not further limit claim 28 because the mammal may already have MDE activated. The distinction between "embryonic" and "fetal" is unclear and the metes and bounds of "early" postnatal development cannot be determined for reasons cited above. Furthermore, it appears that the method is missing the step of repressing MDE expression until adulthood which is essential to obtain the desired phenotype.

Claim 46 is indefinite. Claim 46 may not further limit claim 36 because the mammal may already have MDE activated. The distinction between "embryonic" and "fetal" is unclear

and the metes and bounds of "early" postnatal development cannot be determined for reasons cited above.

Claim 49 is indefinite. Claim 49 may not further limit claim 41 because the mammal may already have MDE activated. The distinction between "embryonic" and "fetal" is unclear and the metes and bounds of "early" postnatal development cannot be determined for reasons cited above. Furthermore, the phrase "the collagenase" lacks antecedent basis.

Claims 52-54 are indefinite. Step (a) may not further limit claim the mammal in claims 28, 36 or 41 because the mammal may already have MDE activated. Furthermore, if applicants intend to include the method by which the mammal is made, step (a) is missing the step of repressing MDE expression until adulthood which is essential to obtain the desired phenotype. The distinction between "embryonic" and "fetal" is unclear and the metes and bounds of "early" postnatal development cannot be determined for reasons cited above. The metes and bounds of the phenotype encompassed by step (a) cannot be determined. It is unclear whether the phrase encompasses a mammal over a period of time as it develops a characteristic of osteoarthritis or a mammal having a characteristic of osteoarthritis. Step (b) implies the mammal is observed over a period of time as it develops a characteristic of osteoarthritis, but the mammal may already have a characteristic of osteoarthritis in step (a). Step (c) is indefinite because it does not clearly refer to the characteristic or the mammal observed and does not clearly describe the control mammal. What are the metes and bounds of the phenotype of the control mammal? Is it transgenic? Step (c) is indefinite because the phrase "any difference in the nature or extent of the

phenotype change, or any difference in the time required for the phenotypic change to develop" is unclear. It is unclear how to determine the "difference" in a phenotypic "change". It is unclear whether the test requires comparing the development of osteoarthritis in the test and control mammals, comparing a characteristic of osteoarthritis over period of time in the test and control mammals, or comparing a characteristic of osteoarthritis at a specific time in the test and control mammals. Finally, the test requires determining a change in phenotype; however, the claim states any "change" indicates the composition may counteract osteoarthritis. The composition may in fact change the mammal by increasing osteoarthritis; therefore, a mere change in phenotype does not indicate the composition counteracts osteoarthritis as claimed.

The claims appear to be free of the prior art of record.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER